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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,606	02/27/2004	Mary E. Brunkow	601117-109	9642

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EXAMINER	
XIE, XIAOZHEN	
ART UNIT	**PAPER NUMBER**
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,606	BRUNKOW ET AL.	
	Examiner	Art Unit	
	Xiaozhen Xie	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-100* is/are pending in the application.

4a) Of the above claim(s) *97-100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's amendment of the claims on 28 August 2006 is acknowledged.

Upon the Pre-Appeal Brief Review decision, the instant application is re-open for prosecution. Claims 88-100 are pending. Claims 97-100 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 88-96 are under examination in this office action.

Oath/Declaration

The objection to the oath or declaration for non-initialed and/or dated alterations is withdrawn in response to the submission of a new oath.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 88-96 are rejected under 35 U.S.C. § 112, first paragraph, as being lack of full enablement.

Applicant previously argued that determining whether antigen amino acid substitutions resulting from variations in the polynucleotide sequences of SEQ ID NOs: 1, 5, 9, 11, 13 and 15 affect antibody binding would not be undue experimentation. Applicant argued that the specification describes the preparation of antigens as well as

the production and testing of antibodies, and that one of skill can routinely identify or construct any antibody molecules meeting the limitations of the claims, and test them for binding to polypeptides encoded by polynucleotides that are at least 90% identical to SEQ ID NOs: 1, 5, 9, 11, 13 and 15, or that hybridize to one of those polynucleotides. Applicant further argued that Bowie et al., Geysen et al. and Colman references support the conclusion that many substitutions in the antigen encoded by polynucleotides having at least 90% identical to SEQ ID NOs: 1, 5, 9, 11, 13 and 15 are possible without affecting protein folding or antigen binding properties. In a request for a pre-Appeal Conference, Applicant submitted argument that the Examiner's previous statement of "one of skill would evaluate all non-exempted TGF-β binding proteins for antibody binding activity" is not a legal requirement. Applicant argues that *Wands* does not support or require the Examiner's interpretation that one would evaluate all non-exempted TGF-β binding proteins. Applicant argues that in a later advisory action, the Examiner changed the previous statement, and states that "one of skill has to evaluate any non-exempting antibody for binding specificity", which is exactly what is permitted under *Wands*. Applicant argues that because of changing the testing ("all" versus "any"), Applicant has no guidance on how to overcome this rejection.

Applicant's arguments have been fully considered. Upon further review, the rejection of claims 88-96 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement, is maintained.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404

(Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The instant claims are drawn to: 1) an isolated antibody or binding fragment thereof which binds to a TGF-β binding protein, wherein said binding protein comprises a polypeptide encoded by a first polynucleotide (coding sequence) that specifically hybridizes under conditions of high stringency to a second polynucleotide (non-coding sequence), wherein the second polynucleotide comprises a polynucleotide sequence that is fully complementary to a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 9, 11, 13 and 15 (coding sequence), or a complementary sequence thereof (non-coding sequence) which encodes a TGF-β binding protein; and 2) an isolated antibody or antigen binding fragment thereof which specifically binds to a TGF-β binding protein, wherein said binding protein comprises a polynucleotide encoded by a polynucleotide having at least 90% identity to a full length sequence selected from SEQ ID NOs: 1, 5, 9, 11, 13 and 15, or a complementary sequence thereof. The claims are broad in that they encompass a genus, i.e. isolated antibodies or antigen binding

fragments thereof which bind to variants and fragments of TGF-β binding protein, including having deletion, substitution or insertion of one or plural amino acid residues in the sequence. The specification discloses TGF-β binding protein having the sequence as set forth in SEQ ID NO: 1, 5, 9, 11, 13 and 15, and antibodies that bind to the polypeptides. The specification, however, has not provided teaching for the genus of polypeptides that have the functional characteristics as "TGF-β binding protein", nor for antibodies that binds to such a large genus of the polypeptides. The recited hybridization condition in claim 88, i.e., hybridizing at 45°C and washing at 45-50°C, is not stringent known in the art, allowing highly structural changes. Further, the recitation of "a complementary sequence thereto" in claims 88 and 89 is directed to a sequence or fragments thereof complementary to the coding sequence of SEQ ID NO: 1, 5, 9, 11, 13 and 15, and the resulting amino acid sequences are highly variant or completely different from the claimed polypeptides. The specification fails to teach the correlation regarding structure and function, such as what amino acid residues or domains are required for the polypeptide to possess the TGF-β binding protein function, or what amino acid changes will not destroy the characteristics of the protein. Cook et al. (J. Biol. Chem., 2005, Vol. 280(48):40177-186) teach that the modern transforming growth factor β superfamily consists of 42 encoded ligand subunits, five binding receptors (RII), and seven signaling receptors (RI) (see 1st paragraph in Introduction). Keller et al. (Nat. Struct. Mol. Biol., 2004, Vol. 11(5):481-488) teach that BMP signaling requires the binding of two types of receptor serine/threonine kinases: the 'wrist' epitope of BMP-2 binds BMP receptor type IA (BRIA) and type IB (BRIB), whereas the 'knuckle' epitope

binds BMP receptor type II and activin receptor type II. The interaction of BMP with the receptor chains is under stringent control of modulator proteins that bind to the ligand and, by blocking it, prevent receptor activation and signaling. These proteins form three distinct families, the noggin, chordin-SOG and DAN-cerberus families (1st paragraph in Introduction). Apparently, TGF-β binding proteins include a large number of structurally distinctive members. Applicant has provided little or no guidance as to how to make antibodies against such a large genus of polypeptides. The specification provides only general guidance regarding how to make and test antibodies, however, there is no correlation between structure and function. The amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate prediction of a polypeptide's structure from mere sequence data are limited. The divergent structures of the polypeptides represent highly variant antibody specificity. The prior art teaches that particular regions of an antigen can tolerate only relatively conservative substitutions or no substitutions for the antigen-antibody interaction. To determine such a structural correlation to antigeneicity requires undue experimentation, and this is exactly the Bowie et al., Geysen et al. and Colman references have taught.

Since the claims encompass antibodies against variants of TGF-β binding proteins, the lack of direction/guidance presented in the specification regarding which structure features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art

which establishes the unpredictability of the effects of mutation on protein structure and function, it would require undue experimentation for the artisan to practice the claimed invention.

Claims 88-96 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Applicant argues the class of polynucleotides encoding TGF-β binding proteins is readily determinable based on provision of SEQ ID NO: 1, 5, 9, 11, 13 and 15, and Applicant needs not disclose the chemical structures. Applicant argues that the claim language is comparable to that of U. S. Patent No: 6,562,949, which recite the % identity of an amino acid sequence in the claim.

Applicant's arguments have been fully considered but have not been found to be persuasive.

As stated above and previously, the claims are drawn to a large genus, i.e., isolated antibodies or antigen binding fragments thereof which bind to variants and fragments of TGF-β binding protein, including having deletion, substitution or insertion of one or plural amino acid residues in the sequence. Applicant has disclosed one species, the polypeptides encoded by SEQ ID NOs:1, 5, 9, 11, 13, 15 and antibodies that bind to the polypeptides, but has not disclosed sufficient species for the genus as broadly claimed. The specification does not define any structural features commonly possessed by members of the genus that distinguish them from others. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient

to enable one of skill to isolate and identify polypeptides encompassed. One skilled in the art, therefore, cannot, as one can do with a fully described genus, recognize the identity of the members of the genus. A definition by function does not suffice to define the genus because it is only an indication of what property the protein has, rather than what it is. Further, the instant claim language is not comparable to that of U. S. Patent No: 6,562,949, which recites the % identity of an amino acid sequence that binds a semaphorin selected from the group consisting of A39 semaphorin and AHV semaphorin. The polypeptides of the instant invention have different structural or correlative teachings from the '949 patent.

Double Patenting

The rejection of claims 88-96 under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of U. S. Patent No: 6,803,453, is maintained. Applicant indicated in the response dated 8 March 2006 that a terminal disclaimer will be filed upon indication of allowable subject matter in this application.

Conclusion

NO CLAIM IS ALLOWED.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
February 16, 2007

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